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October 25, 2016

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2016-D-2153: Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices; Draft Guidance for Industry and Food and Drug Administration Staff; Availability

To Whom It May Concern:

The Advanced Medical Technology Association ("AdvaMed") appreciates the opportunity to provide comment on the Food and Drug Administration's ("FDA" or "Agency") Draft Guidance for Industry and Food and Drug Administration Staff: Use of Real-World Evidence ("RWE") to Support Regulatory Decision-Making for Medical Devices ("Draft Guidance").[1] AdvaMed represents manufacturers of medical devices, diagnostic products, and health information systems that are transforming health care through earlier disease detection, less invasive procedures, and more effective treatment. Our members range from the smallest to the largest medical technology innovators and companies.

AdvaMed is optimistic about the potential beneficial uses of RWE. As the National Evaluation System for Health Technology ("NEST") begins its work, understanding FDA's potential use of the data is helpful. While this Draft Guidance provides an initial understanding of how the Agency may use RWE in regulatory decision-making, we believe additional information is needed. Below we provide our general comments concerning the content of the Draft Guidance. A more comprehensive list of detailed comments regarding the Draft Guidance can be found in the attached document.

1. The Scope of the Draft Guidance Should Be Expanded

The Draft Guidance is heavily focused on device registry data. There are numerous additional data sources that could provide the Agency with RWE, such as insurance claims databases and electronic health records. The Draft Guidance is also primarily focused on Class III and implantable devices, likely due to its predominant focus on devices subject to a registry. FDA should clarify the application of the Draft Guidance to Class II devices that are not subject to a registry. We also note that the Draft Guidance does not explain how it

[1] Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices; Draft Guidance for Industry and Food and Drug Administration Staff; Availability (July 27, 2016), *available at* http://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf.

can be applied to in vitro diagnostic devices ("IVD"). IVDs are not referenced in the document, and no IVD-specific examples are provided.

Moreover, we believe it is important for FDA to clarify and provide examples regarding how RWE can support regulatory decision-making for Class II products in the pre-market phase of a device's development. As currently written, the Draft Guidance does not address the use of RWE for pre-market regulatory decision-making for non-registry devices. Instead, the only potential use of RWE for class II devices described in the Draft Guidance concerns post-market compliance monitoring.

2. Additional Information and Examples Should Be Included

We recommend FDA provide additional information and examples to support a more robust picture of the Agency's potential use of RWE. For example, the Draft Guidance should address how RWE can be leveraged to bring new devices to the market faster. FDA officials have repeatedly expressed the Agency's intent to leverage RWE to bring new, innovative devices to market faster by shifting some of the premarket data collection burdens to the postmarket phase.[2] However, the Draft Guidance does not address this possibility.

3. FDA Should State How It Will Weigh Various Data Sources

FDA describes in the Draft Guidance several sources of RWD and identifies several properties and questions that the Agency will assess when determining data quality or applicability to various regulatory decisions. The value and usefulness of the Draft Guidance would be improved by defining and including the associated framework for how FDA proposes to score and weight these various data elements for quality and impact in the overall decision making process, including data collected from international markets. Failure to provide a scoring or weighting framework reduces the value of the draft guidance, as it does not promote transparency and consistency. Without this detail, decisions take on a subjective nature and are likely to be inconsistent across FDA and within industry.

4. Clarify the Application of Informed Consent

Although the Draft Guidance discusses the application of IDE requirements and touches upon informed consent, we believe more explicit guidance for FDA staff and industry is necessary to avoid conflating the use of RWE and RWD with the collection of research data when studying an investigational device. RWD related to approved or cleared devices used in clinical practice does not become research data, subject to informed consent, simply because it is repurposed for use in another setting. Clearly distinguishing the use of a test article, where consideration of informed consent is appropriate, from approved or cleared devices used in clinical practice will benefit FDA staff and industry in the application and understanding of RWE. While we believe the guidance appropriately advises consideration of federal, state and local laws, reference to privacy protections is more appropriate than human subject protections. The use of health care data as governed under statutes, such as

[2] *See, e.g.*, JAMA. 2016;316(11):1153-115, Need for a National evaluation System for Health Technology (Sept. 20, 2016), *available at* http://jamanetwork.com/journals/jama/article-abstract/2533407.

the Health Insurance Portability and Accountability Act ("HIPAA"), is more applicable to RWE than human subject protections designed to address studies of investigational devices. Clear guidance and understanding of this aspect at the inception of RWE policies is an important step to establishing an RWE system.

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AdvaMed would like to thank the FDA for its consideration of these comments. Please do not hesitate to contact me at 202-434-7224 or zrothstein@advamed.org if you have any questions.

Respectfully submitted,

/s/

Zachary A. Rothstein, Esq.
Associate Vice President
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Attachment

AdvaMed Comments

Use of Real-World Evidence to Support Regulatory Decision-Making: Draft Guidance

#	Line No.	Comment/Proposed Change	Rationale
	97	We recommend revising the sentence to read: ". . . that can be used in FDA regulatory decision-making for medical devices, including software as a medical device and combination products with a device primary mode of action."	We believe this clarification will aid the reader's understanding of the Agency's intent.
	99-116	Include: "published literature."	Published literature is an important source of RWE. For example, literature may be used to demonstrate the clinical validity of an IVD biomarker.
	99-116	Include: "curated databases."	Curated databases are an important source of clinical validity information. *See, e.g.*, FDA Draft Guidance, Use of Public Human Genetic Variant Databases to Support Clinical Validity for Next Generation Sequencing (NGS)-Based In Vitro Diagnostics.
	117-119	We recommend FDA clarify when an IDE application is required to be submitted when data is collected retrospectively.	This change will will help clarify the Draft Guidance.
	119-122	Revise the text as follows: "However, this guidance does not address the use of non-clinical data and adverse event reports ~~and secondary use of clinical trial data (e.g., post hoc analyses)~~."	The Draft Guidance discusses retrospective studies at length, and the secondary use of clinical trial data appears to fall within the definition of "Retrospective Study" that is provided on page 21.
	141-145	We recommend FDA identify circumstances in which RWE is either not relevant or should not be considered.	This addition will help clarify the Draft Guidance.
	142-143	This sentence should be re-written.	As currently drafted, it is not clear what the sentence is attempting to convey.
	150-151	We recommend adding "patient preference information" to the list of guidance documents that FDA has issued that balance premarket and postmarket data collection.	Patient preference information is another source of RWE that FDA considers.
	154-158	We recommend clarifying that the listed benefits are a *potential* outcome of the national evaluation system.	The national evaluation system is still in its infancy and it is not clear all of these benefits will result.

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	200-201	Revise to: "RWE has the potential to contribute to a fuller understanding of the benefits and risks to patients and their preferences when using a medical device."	Patient preference information can help identify the most important benefits and risks of a technology from a patient's perspective.
	203-210	We recommend FDA provide examples, metrics, and/or criteria that might assist institutions in refining their data entry practices so that such data sources more readily meet FDA's expectations of quality and reliability.	The Draft Guidance currently states that RWE may be limited in its appropriateness for regulatory use due to the underlying quality and reliability of the collected data. It would be helpful if the Agency provided recommendations for items such as format, level of information, and criteria that institutions may use in their data entry practices. Such statements may promote a uniform approach across multiple institutions.
	219-223	We recommend FDA clarify whether it is possible to mitigate potential biases that may exist in retrospective analysis of RWE, and under what circumstances a prospective or traditional clinical trial would be needed to support retrospective analysis of RWD.	The Draft Guidance appears to assume that there are mechanisms to remove or mitigate potential biases in a retrospective study or analysis.
		We recommend FDA specifically indicate whether a data analysis plan should be finalized before the beginning of any analysis.	The use of terms "prospective" and "retrospective" in reference to an analysis is not well-defined in the Draft Guidance, which could lead to confusion. For example, the sentence beginning on Line 219 could be read as indicating that a retrospective analysis of a medicinal product registry is inherently biased and should not be used, and that a new registry should be initiated for each research question.
	221-222	We recommend FDA describe in more detail the key elements of a prospective analysis plan.	The Draft Guidance only provides the minimum elements needed in a prospective analysis plan.
	221-229	We recommend the following revisions: "Therefore, at a minimum, a prospective analysis plan is needed for data analysis (but not to collect the data) and, in some circumstances, a prospective trial or a traditional clinical trial may be necessary to generate sufficient evidence for a regulatory decision . . . . Ultimately, RWD ~~collected~~ analyzed using a prospective trial design may be used to generate or contribute to the	These changes clarify that a prospective plan is not required to gather data, but rather to mine or analyze that data.

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		totality of evidence needed to assess medical device performance if the sources of bias can be sufficiently mitigated."	
	229-230	We recommend the following revision: ". . . this will require that the RWD sufficiently capture detailed device ~~identifiers~~ identification information and other relevant variables to facilitate the analysis . . . ."	We believe "device identifiers" is too specific because it implies compliance with the Agency's UDI rules. Other valuable information may be gathered from legacy medical devices that do not have a UDI or other devices otherwise exempt from the UDI rules.
	244-247	We recommend the following revisions: ". . . it is important that the data not only follow the criteria described in section V, but that the results are also presented to FDA in a standardized file format and data structure . . . as data would be presented from traditional clinical trials."	This change would clarify that the data, as obtained from a registry or other sources of information, do not need to meet the format of a traditional clinical trial.
	253	Delete: "clinical."	By FDA's own definition, not all RWE will consist of clinical data.
	273-274	We recommend adding: "RWE, including literature and curated databases, may provide sufficient evidence to demonstrate the clinical validity of an IVD biomarker."	This addition helps explain how RWE may be used to advance IVD innovation.
	273-274	We recommend adding: "conversion of an HDE to a 510(k) or PMA."	The collection of RWD during the life span of an HDE makes it a promising candidate for the use of RWE to convert the HDE into a 510(k) or PMA, particularly when the device has been available as an HDE for several years.
	285-289	The Draft Guidance should provide examples of when a device might be used in a population that is more specific than the one listed on the label.	This information will help clarify the Draft Guidance.
	293-294	We recommend the following revision: ". . . ongoing surveillance will result in the identification of a signal that, upon further root cause investigation, may suggest~~s~~ there is an issue with a medical device."	Ongoing surveillance may not always require collection of additional data, depending on the nature of its root cause.

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	306-307	We recommend FDA provide additional detail and examples regarding the use of RWE instead of submitting Medical Device Reports (MDRs).	This is an important aspect of the use of RWE, and additional information and clarity would be helpful.
	306-307	Insert: "registries."	The potential for a registry to take the place of MDRs would be an important consideration before the creation of a particular registry.
	311	We recommend adding the following item to this list: "To reclassify a medical device to a lower risk classification."	This is consistent with the Agency's prior use of RWE (*e.g.*, to down-classify ECMO devices from Class III to Class II Special Controls).
	350	Please add Footnote 17 to the document.	The footnote is currently missing.
	358	We recommend FDA provide specific guidance on implementing Informed Consent Requirements (21 C.F.R. § 50) in existing real world registries. Current data collection on recognized platforms does not require informed consent and the necessity to obtain specific informed consent would put limitations in place similar to a traditional clinical study instead of RWD collection. However, it is appropriate in other circumstances to obtain Informed Consent (or waiver) even when de-identified data is collected.	Conformance to Informed Consent in existing real world registries is difficult. Additional clarity is required.
	367	Provide additional clarity on the requirements for verifiable source documentation and data monitoring practices.	As a Sponsor, the use of existing real world registry platforms to support regulatory decision-making is appealing. However, existing registry platforms are independent from manufacturers and the data monitoring practices may not be as well established as in traditional clinical studies. These practices are currently dictated by the existing registry society/governance.
	370	We recommend the following addition: ". . . imaging data, patient preference information, patient-reported . . . ."	Patient preference information may be a relevant source of patient based RWE in determining benefit/risk.
	367-372	We are concerned that FDA does not refer to the Draft Guidance on the Use of Electronic Health Record Data in Clinical Investigations (May 2016), including addressing the comments raised by the AdvaMed comments.	AdvaMed's comments in response to the draft guidance are available here.

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	372	Insert after UDI: "as appropriate."	Some devices are not subject to the UDI regulations.
	384	For situations in which multiple sources of RWE exist for a device, FDA should explain the order of preference/regulatory purpose for each source, or whether the concurrent use of multiple sources of high quality data can strengthen the evidence.	Further detail will provide clarity and ensure a more consistent application of RWE, particularly when planning pre-submission meetings.
	392-395	FDA should provide additional detail regarding the responsible party for disclosing certain attributes of a dataset.	Most registries are not owned or governed solely by the study Sponsor. FDA should clarify whether the Sponsor has an obligation to answer questions about registry data validation, attributes, etc.
	418-420	When case reports are the main source of RWE, FDA should clarify whether multi-centered case reports will be required to ensure representativeness and generalizability of data.	Single case reports may not represent or summarize the data, as they tend to be very specific to certain small patient populations and/or targeted rare uses.
	423-424	We recommend FDA clarify whether the percentage captured for patient care encounters is intended to cover all patient usage or only patient usage in the study population.	This clarification will aid the reader's understanding of the Agency's intent.
	426-427	We believe it would be helpful if FDA could provide additional clarity concerning the elements of a validation protocol.	The scope of a validation protocol can vary.
	441	We recommend FDA clarify the phrase, "valid and appropriate analytical methods."	Such clarification will benefit the reader.
	449-452	We suggest FDA provide additional detail on whether sponsors are expected to provide the described documentation as part of the submission and how FDA intends to qualify or evaluate such information.	Additional details for this item would be helpful.
	462	We recommend the Draft Guidance discuss in more detail a prospective analysis plan for a retrospective study (*i.e.*, when data have been collected).	Additional details for this item would be helpful.
	488-490	We believe it would be helpful if FDA could provide additional clarity concerning the elements of analysis design.	Particular design decisions are common to many prospective protocols. Understanding FDA's preferences will help with such decision-making.

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	501	We recommend FDA provide additional information regarding how changes to data should be tracked and managed.	Without adequate protocols, data integrity and assurance cannot be confirmed.
	527	We recommend deleting: "This type of verification is equally important for RWD that is intended to be used for regulatory analyses."	It may not be possible to compare data from research to source documents through audits, as is done in traditional clinical research, because access to those documents may be limited.
	537-671	We recommend FDA provide examples involving the retrospective analysis of RWD to generate RWE.	Most of the examples provided in Section VI focus on the prospective collection of RWD to generate RWE for use in regulatory decision-making. However, as identified in the Draft Guidance, retrospective analysis of data may also play a significant role in regulatory decision-making and is part of the RWD definition. As such, it would be helpful if FDA could share more examples where retrospective RWD may be utilized to generate RWE.
	537-671	We recommend FDA include examples that involve non-implantable devices, devices that are class II, and IVDs.	Most of the examples provided in Section VI involve Class III, implantable devices. The vast majority of medical devices in the marketplace are class II and non-implantable. Industry and FDA staff would benefit from examples for these other devices.
	540	FDA should provide additional details describing how manufacturers can utilize RWE that was collected during off-label uses.	Additional details for this item would be helpful.
	540	We recommend that FDA provide additional information on sub-populations.	While the Draft Guidance describes the use of RWD for expanding indications for use, it would be beneficial to add information concerning the use of RWD for claims related to sub-populations. It is likely that in most cases, the public health risk related to claims in sub-populations are smaller than the public health risks related to expanded indications for use.
	572-590	We recommend FDA include a reference regarding whether the registry was under an IDE, as such information is included in other examples.	This reference would bring clarity regarding when an IDE is required.

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	714	We recommend FDA clarify that the terms "prospective" and "retrospective" refer to the study design to avoid misinterpretation.	The Draft Guidance uses the terms "prospective" and "retrospective" for the design analysis time-point rather than the study design.
	747	We appreciate FDA providing a definition for "traditional clinical trial." However, we recommend the Agency distinguish between "large simple trial" and "pragmatic clinical trial."	These terms are used in the Draft Guidance but are not defined in the Glossary.